REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Claim 1 has been amended to more specifically define the formic acid derivative referred to by the term "a reactive derivative thereof," as further discussed below with respect to the to the Examiner's rejection under 35 USC § 112.

Claims 4-8 remain as previously amended, and claims 2-3 and 9-29 were previously cancelled as being non-elected.

New Claims 30 to 52 have been added to more particularly claim various process details, in particular aspects of the "one-pot procedure" that is described, *e.g.*, in the last paragraph on page 4 of the description and in Example 1, wherein an organic solvent (*e.g.*, methylene chloride) solution of the 2-aminobenzonitrile of Formula IV is separated from step (a) and added to a polar protic solvent for step (b), and for the solution of the 2-aminobenzamide of Formula V in a polar protic solvent formed in step (b) is used in the cyclisation reaction of step (c). In other words, the intermediates of Formula IV and/or of Formula V are not isolated as such but are obtained, and used in the next step, as a solution in the appropriate organic solvent as discussed in the last paragraph on page 4 and in original claim 4, and exemplified in Example 1.

The multistep process of Claim 1 is directed to the transformation of the 2-nitrobenzonitrile of Formula III by way of the 2-aminobenzonitrile of Formula IV and the 2-aminobenzamide of Formula V to give the quinazolinone of Formula II. The starting material of Formula III and the intermediate compound of Formula IV are novel compounds. The intermediate compound of Formula V is known from Japanese Patent Application No. 11292855 as acknowledged in the specification on page 5, at lines 6 to 10.

New Claim 30, dependent on claim 1, further defines step (a) as being carried out in the presence of a water-soluble inorganic reducing agent to prepare the intermediate of Formula IV and its extraction into an organic solvent for use in step (b). Support for this

aspect of the process is found in the specification on page 3, at lines 22 to 24, on page 4, at lines 30 to 31, original claim 5 and in Example 1 on page 10, at lines 11 to 16.

New Claim 31, dependent on Claim 1, further defines step (a) as being carried out in the presence of the water-soluble inorganic reducing agent sodium dithionite to prepare the intermediate of Formula IV and its extraction into the organic solvent methylene chloride for use in step (b). Support for this aspect of the process is found in the specification on page 3, at lines 22 to 24, on page 4, at lines 30 to 31, and in Example 1 on page 10, at lines 11 to 16.

New Claims 32 and 33, dependent on Claim 1, further define the conditions for process step (b) for each of which there is support in the specification on page 4, at lines 9 to 12, and in Example 1 on page 10, at lines 23 to 31.

New Claim 34, dependent on Claim 1, provides further detail for the conditions for process step (b) for which there is support in the specification on page 4, at lines 9 to 12, and in Example 1 on page 10, at lines 23 to 31.

New Claim 35, dependent on Claim 1, further provides that the intermediate of Formula IV formed in step (a) is not isolated as such, but rather is extracted with an organic solvent, which organic extract is added to a polar protic solvent and extracting organic solvent is removed by distillation, and the resultant solution of the intermediate of Formula IV in the polar protic solvent is used in the hydration of step (b). Support for this claim is found in the specification as noted in relation to new claim 30 above and in Example 1 on page 10, at lines 11 to 16 and at lines 23 to 28.

New Claim 36, dependent on Claim 1, provides for similar processing of the intermediate of Formula IV as in Claim 35 and specifies particular suitable organic solvents.

New Claim 37, dependent on claim 1, further provides that the intermediate of Formula V formed in step (b) is not isolated as such, but is prepared and used in the subsequent cyclisation reaction of step (c) as a solution in a polar protic solvent. Support for this claim is found in the specification at page 4, at lines 30 to 31, and from Example 1 on page 10, at lines 26 to 31, and on page 11, at line 12.

New Claim 38, dependent on Claim 1, provides for similar processing of the

intermediate of Formula V as in Claim 37 and specifies *tert*-amyl alcohol as the organic solvent.

New Claim 39, dependent on Claim 1, arises from the merging of the subject matter of Claims 35 and 37, and specification support therefore is as provided above with respect to Claims 35 and 37.

New Claim 40, dependent on Claim 1, arises from the merging of the subject matter of Claims 36 and 38, and specification support therefore is as provided above with respect to Claims 36 and 38.

New Claims 41 and 42, dependent on Claim 1, further provide that the cyclisation reaction in step (c) of the 2-aminobenzamide of Formula V into the quinazolinone of Formula II is carried out under acidic conditions (Claim 41) and that step (c) is acidified with formic acid (Claim 42). Support for the use of acidic conditions, and specifically formic acid, in step (c) is found in the specification at page 4, at lines 26 to 28, and in Example 1 on page 11, at line 12.

New dependent Claim 43, dependent on Claim 1, further provides that the cyclisation reaction in step (c) of the 2-aminobenzamide of Formula V into the quinazolinone of Formula II is carried out in the presence of an excess of formamide, which acts as a reactant and as a solvent. Support for the presence of an excess of formamide in the cyclisation reaction of step (c) is found in the specification on page 4, at lines 23 to 25, and in Example 1 on page 11, at lines 14 to 15.

New Claim 44, dependent on Claim 1, further provides that the cyclisation reaction in step (c) of the 2-aminobenzamide of Formula V into the quinazolinone of Formula II is carried out at a temperature at or near 100°C. Support for the reaction temperature recited in this claim is found on page 4, at lines 26 to 28.

New Claim 45, dependent on Claim 1, further provides that the cyclisation reaction in step (c) of the 2-aminobenzamide of Formula V into the quinazolinone of Formula II is acidified with formic acid, that the resultant mixture is concentrated by distillation under reduced pressure and an excess of formamide is added to act as a reactant and as a solvent. Specification support for these further process steps and conditions is found on page 4, at lines 23 to 25, and in Example 1 on page 11, at lines 12

to 15.

New Claim 46, dependent on Claim 1, further provides that the cyclisation reaction in step (c) of the 2-aminobenzamide of Formula V into the quinazolinone of Formula II is acidified with formic acid, that the resultant mixture is concentrated by distillation under reduced pressure and an excess of formamide is added to act as a reactant and as a solvent, and that the reaction is carried out at a temperature at or near 100°C. Specification support for these further process steps and conditions is found on page 4, at lines 23 to 28, and in Example 1 on page 11, at lines 12 to 15.

New Claim 47, dependent on Claim 1, arises from the merging of the subject matter of Claims 37 with aspects of Claims 42 and 43 and subject matter from Example 1 on page 11, at lines 12 to 15. Specification support therefore is as provided above with respect to Claims 37, 42 and 43 and Example 1.

New Claim 48, dependent on Claim 1, arises from the merging of the subject matter of Claims 38 with aspects of Claims 42 and 43 and subject matter from Example 1 on page 11, at lines 12 to 15. Specification support therefore is as provided above with respect to Claims 38, 42 and 43 and Example 1.

New Claim 49, dependent on Claim 1, arises from the merging of the subject matter of Claims 30 and 47, and specification support therefore is as provided above with respect to Claims 30 and 47.

New Claim 50, dependent on Claim 1, arises from the merging of the subject matter of Claims 31 and 48, and specification support therefore is as provided above with respect to Claims 31 and 48.

New independent Claim 51 arises from the introduction of process details into the process of Claim 1. The subject matter added concerning process step (a) comes from Claim 30 (for which there is support from the specification on page 3, at lines 22 to 24, on page 4, at lines 30 to 31, and in Example 1 on page 10, at lines 11 to 16) and from Claim 35 (for which there is support from Example 1 on page 10, at lines 23 to 28). The subject matter added concerning process step (b) comes from Claim 7 (for which there is support from the specification on page 4, at lines 9 to 12) and from Claim 37 (for which there is support from page 4, at lines 30 to 31, and from Example 1 on page 10, at lines

26 to 31, and on page 11, at line 12). The subject matter added concerning process step (c) comes from Claim 45 (for which there is support from page 4, at lines 23 to 25, and in Example 1 on page 11, at lines 12 to 15).

New independent Claim 52 arises from the introduction of certain preferred process details into the process of Claim 1. The subject matter added concerning process step (a) comes from Claim 31 (for which there is support from the specification on page 3, at lines 22 to 24, on page 4, at lines 30 to 31, and in Example 1 on page 10, at lines 11 to 16) and from Claim 36 (for which there is support from Example 1 on page 10, at lines 23 to 28). The subject matter added concerning process step (b) comes from Claim 34 (for which there is support from the specification on on page 4, at lines 9 to 12, and in Example 1 on page 10, at lines 23 to 31) and from Claim 38 (for which there is support from page 4, at lines 30 to 31, and from Example 1 on page 10, at lines 26 to 31, and on page 11, at line 12), The subject matter added concerning process step (c) comes from Claim 46 (for which there is support from page 4, at lines 23 to 25, and in Example 1 on page 11, at lines 12 to 15).

It should be clear from the above that these amendments and new claims are supported by the specification and claims as filed and no new matter is being added. Therefore, entry of these amendments is believed to be appropriate and is repsectfully requested. These amendments are made without waiver or prejudice to Applicants' right to prosecute any subject matter deleted thereby in one or more continuing applications.

Following entry of these amendments, claims 1, 4-8 and 30-52 are pending in this application.

Specification Amendment-Abstract of the Disclosure

The Examiner has objected to the abstract of the disclosure is because it contains legal phraseology such as "said" and requires correction thereof. One occurance of the term "said" is the only "legal phrasology" found in the abstract and has been removed as required by the Examiner (even though it is believed more clearly identify the "quinazoline derivative" being referred to). Moreover, what the Examiner refers to as "implied" phrases have also been removed, even though the Abstract does not approach the 150 word limit (before or after the amendment). The Abstract as amended is therefore

believed to overcome all grounds for the objection thereto.

Claim Rejections - 35 USC § 112, 2nd Paragraph

Claims 1 and 4-7 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, with respect to the term "derivative" in the claim 1 phrase "with formic acid, or a reactive derivative thereof." The Examiner suggests that claim 1 be amended to include only those reactive derivatives specifically listed in the specification on page 4 to overcome this rejection. Applicants believe that the term "derivative thereof" in the context used in claim 1 would be clear to a person skilled in this art, particularly in view of the guidance provided in the specification passage noted by the Examiner. Nevertheless, Applicants have amended claim 1 to specifically recite these preferred formic acid derivatives in step (c) in order to advance the prosecution of this application to allowance. It is therefore believed that this ground for rejection has been overcome.

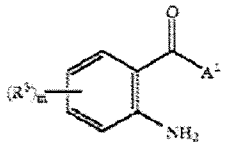
Claim Rejections - 35 USC § 103

Claims 1 and 4-8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US Patent No. 6,294,532 (hereinafter "US '532" in combination with JP 11228515 (hereinafter "JP '515") and WO 02/00649 (hereinafter "WO '649"). The Examiner attached a *machine* translation of JP '515, which will be referenced herein without necessarily endorsing the accuracy thereof.

- US '532 is asserted by the Examiner as disclosing:

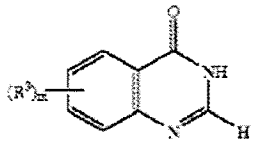
  > ... the compound XVII which can prepare XIV (see column 31, line 5 and column 32, line 15):

(XVII)



and

(XIV)

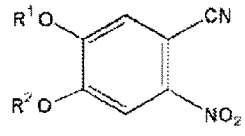


(which corresponds to applicants step (c) and applicants' formulas V and II). When Al is an amino group, formic acid or an equivalent can be utilized to cause cyclisation to obtain formula XIV, column 32 lines 33-48. An equivalent of formic acid is disclosed as formamide, see line 23, column 32. Preferred values for R3 and m are seen on column 7 wherein m is preferably 1 or 3 and X7 is preferably -O-; on column 10 wherein R3 is preferably R15X7; and on column 11 wherein preferred values of R15 include methyl and 3-morpholinopropyl. The compound XIV is an intermediate to prepare compounds of the formula (I) which are useful for the treatment of specific cancers, column 2.

(Action at page 5).

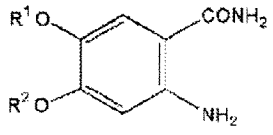
- JP '515 is asserted by the Examiner as disclosing:

  ... the process of preparing (2) from (1):



(1)

and



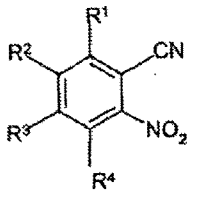
(2)

(which corresponds to applicants steps (a) and (b) and formulas III, IV and V), page 2 of translation. The preparation is useful for preparing anthranilamides useful in the production of medicines (page 1). R1 and R2 can be substituted or unsubstituted alkyl, such as methyl ethyl and propyl, page 3. The process utilizes a palladium catalyst for the hydrogenation and is carried out in the presence of an alkali metal bases such as calcium carbonate in a polar protic solvent such as methanol, page 4.

(Action at pages 5-6).

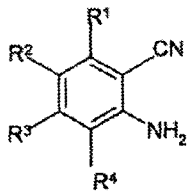
- WO '649 is asserted by the Examiner as disclosing:

> ... the process of preparing compounds of the formula (IX) with compounds of the formula (XIII), page 59 and 57:



(XIII)

and



(IX)

> (which corresponds to applicants step (a)). R2 and R3 can be methoxy or 3- morpholinopropoxy, see page 78 which discloses the use of sodium hydrosulfite as a water-soluble inorganic reducing agent in the preparation of the compound H, see also page 77. Preferences for R2 and R3 are also seen wherein R2 and R3 are X1R9 wherein X1 is oxygen and R9 can be methyl or one of R2 and R3 can be —OC1-5alkylR33 wherein R33 is 3-morpholinopropoxy. The compounds of the formula IX are useful for preparing compounds of the formula (I) which are useful for the treatment of specific cancers, page 3.

(Action at page 6).

The Examiner states at page 7 of the Action that US '532 discloses a process of preparing (XIV) from (XVII), which is asserted to correspond to step (c) of the presently claimed invention, but notes that US '532 does not disclose the compounds of formulae (III) and (IV) or the process steps of (a) and (b) required in each of the present claims.

The Examiner also asserts that JP '515 discloses a process which corresponds to steps (a) and (b) of the presently claimed invention, but notes that JP '515 does not disclose the compound of formula (II) nor process step (c) required in each of the present claims.

The Examiner also asserts that WO '649 discloses a process which corresponds to step (a) of the presentlyclaimed invention, but notes that WO '649 does not disclose steps (b) and (c) required in each of the present claims.

From the above assertions the Examiner concludes that:

> ... minus a showing of unobvious results, the claimed process is no more than a selective combination of prior art teachings done in a manner obvious to one of ordinary skill in the art *since each step of the process appears to be relatively complete in itself and there is no indication of an interaction between steps* of such a type that would lead one of ordinary skill in the art to doubt that a substitution of alternative steps known to the art could be made. In re Mostovych, 144 USPQ 38 (1964). All of the claimed steps (a), (b) and (c) were known in the prior art and one skilled in the art could have combined the steps as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

(Action at pages 7-8; emphasis added).

This ground for rejection is respectfully traversed.

Applicants do not agree with many aspects of the Examiner's interpretation of the above references. In particular, it is respectfully submitted that the Examiner has impermissibly use of hindsight from Applicants' disclosure to make the multiple selections from myriads of choices required to support the assertion that these references separately teach process steps with reactants and resulting products (intermediates) that resemble those of the individual process steps (a), (b) and (c) of the presently claimed process. However, even more significantly, neither these references nor the rejection based thereon address the integrated process sequence formed by the claimed combination of these particular steps, which provides the significant advantages of reduced time and cost particularly in large scale, commercial production as stated on page 2 of the specification:

> We have now devised a suitable process for the manufacture of the compound of Formula I. The new process is advantageous in that it allows the final product to be made in high quality and yield on a large scale. The process is more convergent than the previous routes and allows a substantial reduction in the number of intermediates that must be isolated. This provides significant advantages of time and cost. Chromatographic purification procedures are not required. According to the invention, processes are provided for the manufacture of key intermediates that may be used in the preparation of the compound of Formula I.

(Specification at page 2, lines 7-14). The following remarks will particularly focus on the

fact that neither the cited art nor the rejection address any teaching or motivation to provide the particular claimed integrated process sequence that provides these significant advantages.

Thus it is respectfully submitted that, whether or not the process steps of the present claims considered in isolation resemble process steps that were *separately* known in the art, the presently claimed invention is directed to an *integrated process sequence*. It is this *integration* of one or more of the process steps that "is more convergent than the previous routes and allows a substantial reduction in the number of intermediates that must be isolated," "chromatographic purficiation procedures are not required" and the process thus "provides significant advantages of time and cost" as noted in the above passage from the specification. These advantages are of particular importance for a process, as here, that was developed to be conducted on a commercial scale.

In other words, claim 1 is not just a combination of separate process steps *randomly* chosen from the multiple different ways in which each might be carried out in the art. Rather claim 1 is an unobvious set of *particular* process steps that form the framework for an integrated overall process sequence that permits process simplification and the resulting substantial savings of time and costs relative to the process steps and/or combinations thereof disclosed in the prior art.

The dependent claims build on this claim 1 framework with more detail on the process conditions and reagents: particularly new dependent claims 30-50 that focus on the features whereby steps (a) and (b) are integrated so as to avoid the need to isolate, as such, the intermediate of Formula IV when going from the the reduction of step (a) to the hydration of step (b); and/or whereby steps (b) and (c) are integrated so as to avoid the need to isolate, as such, the intermediate of Formula V when going from the hydration of step (b) to the cyclisation of step (c).

Similarly, new independent process claims 52 and 53 integrate together in single claims the particular process sequence of claim 1 with many of the details from the intervening dependent claims that more specifically define the overall process sequence that provides the significant advantages noted above.

Therefore, it is submitted that the conclusion reached by the Examiner at page 7

of the Action, that "*since each step of the process appears to be relatively complete in itself and there is no indication of an interaction between steps*" (emphasis added), is not accurate, particularly with repect to the new claims presented above, which emphasize the integrated nature of these steps to provide the overall time and cost savings advantages.[1] The Examiner has not indicated any teaching or motivation for the skilled person to select and combine the *particular* process steps that have been applied. Rather, it is apparent from this conclusion that the applied references, and the particular steps chosen from these references and applied to the rejection, were selected with the hindsight of Applicants' disclosure.

As pointed out in the specification, beginning at page 1, line 23, the existing routes to the compound of Formula II are satisfactory for the synthesis of relatively small amounts of the compound but they tend to involve linear rather than convergent syntheses, each requiring the multiple use of chromatographic purification steps and the isolation of a substantial number of intermediates.

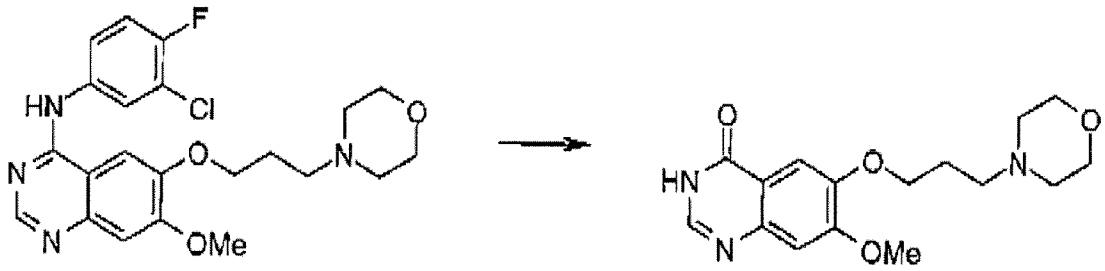
In contrast, the process of the present invention is advantageous in that it allows the final product to be made in high quality and yield on a large scale. The process allows a substantial reduction in the number of intermediates that must be isolated. Rather, each intermediate of Formula IV and V need not be isolated as such but can be prepared and used in the next step as a solution in an organic solvent. This provides significant advantages of time and cost. Chromatographic purification procedures are not required.

The Examiner's attention is drawn to Example 1 on pages 10 and 11 of the present Application, which discloses a large scale synthesis of more than 60 kg of the quinazolinone of Formula II in high yield and without the need for any chromatographic purification steps. It is respectfully submitted that this demonstration of the large scale operation of the presently claimed process provides ample evidence of the significant advantages achieved *vis-a-vis* the prior art methods for the synthesis of the quinazolinone

[1] Claims 1 and 4-9, though not as detailed on the integration as new claims 30-52, when properly construed in light of the specificaiton should likewise be interpreted as providing an overall integrated process sequence rather than the random assortment of individual process steps that the Examiner seems to imply in the rejection.

of Formula II. Neither this integrated process sequence nor the advantages thereby obtained are taught or suggested by the prior art.

For example, one other route to the quinazolinone of Formula II involves cleavage of a 4-anilinoquinazoline form WO 96/33980. Schematically:

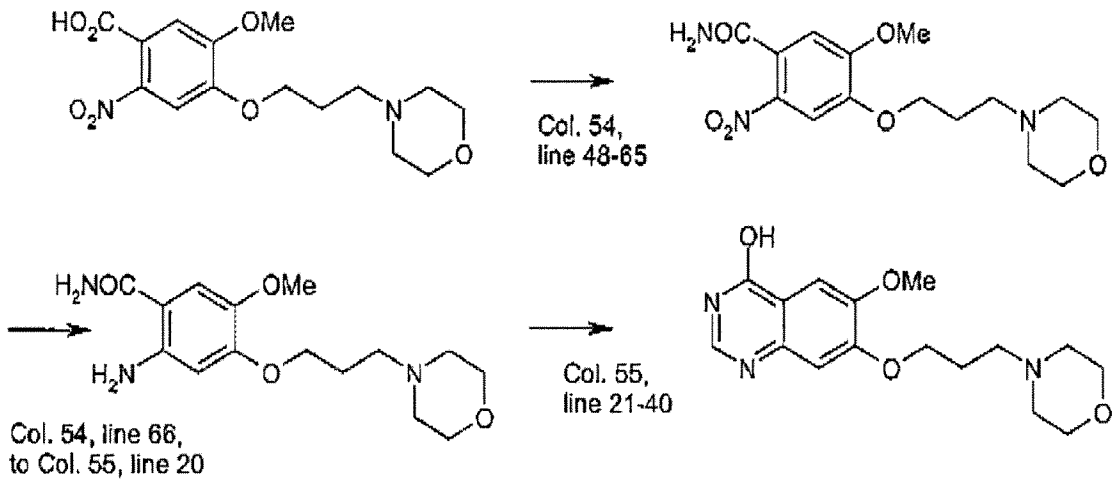


It will be appreciated that this route is wasteful in the sense that the 3-chloro-4-fluoroanilino substituent is removed and discarded.

The Examiner considered that the subject matter of Claims 1 and 4 to 8 was unpatentable pursuant to 35USC 103(a) over the disclosure of US '532 in combination with the teachings of JP '515 and WO '649. Each reference is relied upon for the disclosure of separate process steps that are said to "correlate" at least with respect to the general nature of the reaction, to step (a), step (b) and/or step (c) of the presently claimed process.

However, there is no teaching or suggestion in any of these references that a 2-aminobenzonitrile such as the compound of Formula IV, can be taken from its preparation in reduction step (a), in the form of a solution in an organic solvent that can be introduced into hydration step (b) without intermediate isolation and purification, for conversion to a 2-aminobenzamide such as the compound of Formula V. And there is no teaching or suggestion that this 2-aminobenzamide can be taken from its preparation in hydration step (b), in the form of a solution in an organic solvent that can be introduced into cyclisation step (c) without intermediate isolation and purification, for conversion to the quinazolinone such as the compound of Formula II.

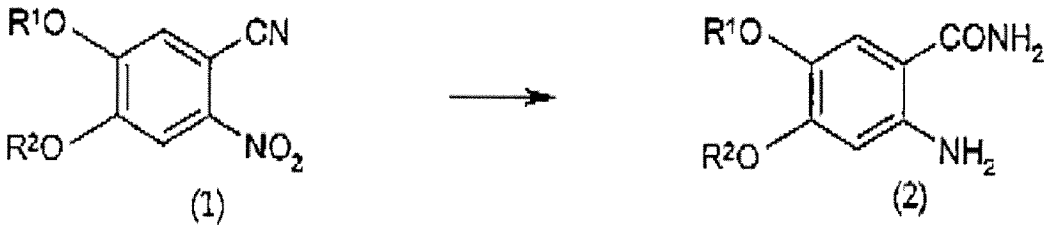
For example, US '532 discloses the following reaction sequence within the portion of example 3 that is concerned with the preparation of starting materials:



A solution of the 2-nitrobenzamide described at Column 54, lines 48 to 65, in the organic solvent THE was concentrated by evaporation, the compound was crystallised from the concentrated solution and was isolated by filtration. A solution of the 2-aminobenzamide described at Column 54, line 66, to Column 55, line 20, in water and hydrochloric acid was concentrated by evaporation to provide a precipitate that was isolated by filtration. Thus, each of the intermediates was isolated and characterised.

Similarly, in WO '649, the reaction scheme disclosed in general Scheme 2 on page 77 that is used in the synthesis of compound 204 involves the 2-nitrobenzonitrile G and the 2-aminobenzonitrile H and several other intermediates, each of which is isolated and characterised.

JP '515 discloses the palladium/barium sulphate/water catalysed conversion of the 2-nitrobenzonitrile compound of the formula (1) to an anthranilamide (2-aminobenzamide) compound of the formula (2) involving two concurrent synthetic steps, namely the hydrogenation of the nitro group and the hydration of the cyano group.



However, each anthranilamide product was obtained as an aqueous solution after removal of the metal catalyst by filtration. The resultant aqueous solution was evaporated and the product was isolated and characterised by NMR spectroscopy and elemental analysis.

In contrast, the process of the present invention allows a substantial reduction in the number of intermediates that must be isolated. Rather, each intermediate of Formula IV and the intermediate of Formula V need not be isolated as such but can be prepared and used in the next process step as a solution in an organic solvent, without intermediate isolation and purification. In the integrated process sequence that is presently claimed, it is only the final product, the quinazolinone of Formula II, which is isolated and characterised.

For this reason alone, it is respectfully submitted that *prima facie* obvious has not been established with respect to the integrated process sequence recited in the present claims, and this obviousness ground for rejection should therefore be withdrawn.

Conclusion

It is believed that the foregoing discussion clearly rebuts the underlying premeses upon which the Examiner based the unobviousness rejection, that "the claimed process is no more than a selective combination of prior art teachings done in a manner obvious to one of ordinary skill in the art" and that "each step of the process appears to be relatively complete in itself and there is no indication of an interaction between steps."

To the contrary, Applicants disclose and presently claim an integrated process sequence wherein the intermediates of Formula IV and/or of Formula V can each be prepared in the form of an organic solution which can be used, withont need for isolation

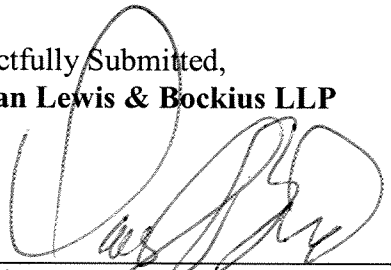
and purification, in the following step. This novel and unobvious feature of the presently claimed invention results in substantial savings in time cost, particularly when the process carried out in a commercial scale. This feature of the invention is particularly highlighted in new claims 30-52.

It is also believed that the objection to the Abstract and the section 112 rejection have been obviated by the above amendments to the specificaiton and claims.

Accordingly, it is believed appropriate and respectfully requested that all ground for rejection be withdrawn and all claim be allowed.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP



Date: August 13, 2008 By: _____

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB: